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(54) Title: TRANSDERMAL THERAPEUTIC SYSTEM WITH FENTANYL OR RELATED SUBSTANCES.

(57) Abstract: The present invention pertains to a transdermal therapeutic system (TTS), comprising a backing layer [Rücksicht in German original is a typo for "Rückschicht" meaning backing layer - Tr.Ed.], which is impermeable to the active ingredient, at least one matrix layer which contains fentanyl or an active ingredient analogous to fentanyl and is based on polyacrylate, and a protective layer to be removed before use, which system is characterized in that the polyacrylate polymer is self-adhesive, free of carboxyl groups and has a saturation solubility for fentanyl of 3 wt.% to 20 wt.%, preferably a saturation solubility of 4 wt.% to 12 wt.% and especially preferably a saturation solubility of 5 wt.% to 10 wt.%, and that the layers containing active ingredient contain at least 80 wt.% of the active ingredient incorporated in a molecularly dispersed, dissolved form.

Transdermal Therapeutic System with Fentanyl or Related Substances

Specification

Fentanyl and substances analogous to fentanyl, such as sulfentanyl, carfentanyl, lofentanyl and alfentanyl, are extremely effective analgesics. The required low dosage and their physicochemical properties, such as the *n*-octanol-water distribution coefficient, the melting point and the molecular weight make possible the transdermal administration of effective quantities of these substances, and their pharmacokinetic properties, such as the rapid metabolism and the relatively low therapeutic index make the transdermal administration desirable.

A TTS with fentanyl as the active ingredient has, indeed, been available commercially for some years. This system is a so-called reservoir system. A reservoir system is defined here as a system that contains the active ingredient in a liquid or gel-like preparation in a pouch formed from an impermeable film, which acts as a backing film, and a membrane that is permeable to the active ingredient, where the membrane is additionally provided with an adhesive layer for attaching the system to the skin. Fentanyl is dissolved in this special case in a mixture of ethyl alcohol and water. Further details of this system can be found in the US Patent Specification No. 4,588,580 and DE Patent Specification No. 35 26 339, both of which contain a more detailed description.

However, reservoir systems have the drawback that the reservoir filling containing the active ingredient comes into contact with the skin over a large area in case of a leak of the reservoir pouch and excessively high doses of the active ingredient are resorbed. This is very dangerous especially in the case of fentanyl and its derivatives, because an overdosage leads to respiratory depression and consequently fatal accidents in a short time. A number of such fatal or nearly fatal accidents were described in *Clinical Pharmacokinet.*, **2000**, 38(1), 59-89.

The object of the present invention was to make available a transdermal therapeutic system with fentanyl or substances analogous to fentanyl which offers the user increased safety against the accidental absorption of overdoses.

This is achieved according to the present invention by using instead of the reservoir system a matrix system, in which the active ingredient is directly incorporated in a self-adhesive polyacrylate and thus it cannot come into contact with the skin over an area larger than that defined by the TTS even in case of damage to the system. In general, the total amount, but at least 80% of the active ingredient is dissolved in this polymer in such a system in the molecularly dispersed form, and the saturation solubility of the active ingredient in the polymer is between 3 wt.% and 20 wt.%. Furthermore, it was surprisingly found that only adhesives free of free carboxyl groups are suitable if polyacrylate adhesives are used to prepare TTS containing fentanyl and its analogs.

In the simplest case, such matrix systems comprise a backing layer, which is impermeable to the active ingredient, a self-adhesive layer containing active ingredient, and a protective layer to be removed before use. A membrane, which controls the release of the active ingredient and is normally also provided with an adhesive layer for attaching the system to the skin, is additionally present in more complicated embodiments of such systems.

The active ingredient-containing layers of such a matrix system according to the present invention

... polyacrylate adhesives that are most suitable are those that have no free functional groups and are prepared only from esters of acrylic acid and/or methacrylic acid and optionally other vinyl compounds without free functional groups, such as vinyl acetate. However, monomers containing free hydroxyl groups, such as 2-hydroxyethyl acrylate or 2-hydroxyethyl methacrylate, can be tolerated during the synthesis of the adhesive in amounts of up to 20 wt.%. Polyacrylates are prepared by free radical polymerization with the use of acrylic acid derivatives and/or methacrylic acid derivatives. Such derivatives are, e.g., esters. Acrylic acid derivatives and methacrylic acid derivatives, especially esters of alcohols containing 1 to 8 C atoms, which optionally contain a hydroxyl group, such as 2-ethyl hexyl acrylate, *n*-octyl acrylate, propyl acrylate, *n*- or *iso*-butyl acrylate, 2-hydroxyethyl acrylate and dimethyl aminoethyl acrylate or the corresponding methacrylates shall be mentioned as examples of such derivatives. Other polymerizable vinyl compounds without free functional groups, e.g., vinyl acetate, may additionally also be used jointly, e.g., in amounts of up to 50 wt.%. The polymers thus prepared are also called stochastic copolymers, because the composition of the polymer chains is determined solely by the distribution of the quantities of the monomers used and by chance.

If the polymers contain free hydroxyl groups, it is possible to additionally crosslink the polymer chains by polyvalent cations, such as Al^{3+} or Ti^{4+} or reactive substances such as melamine. This possibility is taken advantage of to increase the molecular weight and thus to improve the cohesion of the polymers. The possibility of crosslinking polyacrylates, especially polyacrylate adhesives, is especially valuable if the plasticizing action of the active ingredient dissolved in the polymer or the plasticizing action of other inactive ingredients must be compensated. The adhesive is usually used in the form of a solution. The solvents used are, e.g., ethyl acetate, hexane or heptane, ethanol or mixtures thereof. These are removed during the preparation of the TTS.

Table 1 shows the results of permeation studies, which were obtained with an adhesive containing free carboxyl groups and with an adhesive without free carboxyl groups (but without hydroxyl groups). The active ingredient was incorporated in both adhesives at a concentration of 5 wt.%. The permeation study was carried out with Franz diffusion cells, which are known to the person skilled in the art, and with the use of human skin.

Table 1: Results of permeation studies with adhesives with and without free carboxyl groups.

Formulation	Cumulative quantity of permeated active ingredient [$\mu g/cm^2$] Mean value of n = 3*				
	4 hr.	8 hr.	24 hr.	48 hr.	72 hr.
1	0.00	0.00	0.44	1.71	3.51
2	0.0	0.2	4.0	14.7	28.24

*Skin used: Skin from the hypogastric region of women

Formula 1: Polyacrylate adhesive <u>with</u> 4.8 wt.% of free carboxyl groups
Formula 2: Neutral polyacrylate adhesive <u>without</u> free carboxyl groups but with 5.2 wt.% of free hydroxyl groups

... of the rates of permeation attained.

The saturation solubility of the polymer selected for the particular active ingredient is an important property of any polymer containing active ingredient in the TTS technology. This parameter is important because the thermodynamic activity of the active ingredients in the matrix depends on the ratio of the actual concentration to the saturation concentration rather than on the absolute dissolved quantity of the active ingredient in the matrix. Since the active ingredient must be distributed in the skin during the application of the TTS to the skin and activities rather than concentrations will become alike in the process, it is important for reaching the highest possible rate of permeation to select the highest possible thermodynamic activity of the active ingredient in the TTS. This means that the solubility of the active ingredient in the parts of the TTS that contain active ingredient must not be too high, because the concentration of the active ingredient in the TTS must otherwise be rather high to reach a sufficiently high thermodynamic activity. This is not advantageous if the active ingredient present at the high concentration affects the physical properties of the parts of the system that contain active ingredient and/or the active ingredient is very expensive. Both reasons apply in the case of fentanyl, and it should also be additionally borne in mind that fentanyl and its derivatives are narcotics and it is therefore desirable for that reason alone to incorporate as little active ingredient as possible in the TTS or to select the highest possible active ingredient utilization, i.e., the ratio of active ingredient released during the period during which the TTS is being used to the content in the unused TTS.

Based on this criterion, the saturation solubility of the layers containing active ingredient should not be below 3 wt.% nor higher than 20 wt.% for a three-day TTS. The active ingredient utilization becomes too low at higher saturation solubilities even at a high specific permeation rate, and the TTS does not sell well for commercial reasons because of the expensive active ingredient. The saturation solubility is between 4 wt.% and 12 wt.% and especially preferably between 5 wt.% and 10 wt.% for these reasons.

The saturation solubility of fentanyl and its analogues can be additionally reduced by the addition of substances that do not possess good dissolution properties for the active ingredient. Such substances are, e.g., liquid hydrocarbons such as dioctyl cyclohexane, liquid paraffin, hydrocarbon resins such as polyterpenes, especially polypinene, or polar substances such as glycerol, diglycerol and triglycerol or polyethylene glycols, e.g., those with a molecular weight of 200 to 1,000. These substances can form a homogeneous mixture with the polyacrylate adhesive or be contained therein as a separate phase. In particular, glycerol and its derivatives occur in the matrix as a separate phase, e.g., in the form of droplets, already at low concentrations. In particular, the higher saturation solubility in adhesives containing free hydroxyl groups can also be compensated by the addition of such substances.

Table 2 contains some data on the saturation solubility of fentanyl in some of these substances.

Table 2: Saturation solubilities of fentanyl in additives reducing the solubility.

Polyethylene glycol 400	7.5
Glycerol	< 1.5
Diglycerol	< 1.5
Dioctyl cyclohexane	< 1.9
Paraffin, liquid	< 1.5

The effect of such additions can be recognized from comparative permeation studies.

The results of permeation studies with matrices based on a neutral polyacrylate adhesive containing free hydroxyl groups with and without such additives as well as of a polyacrylate adhesive without other free functional groups are compared in Table 3. All formulations contain fentanyl at a concentration of 5 wt.%.

Table 3. Comparative permeation studies with formulations with and without additives lowering the solubility.

Formulation	Cumulative quantity of permeated active ingredient [μg/cm²] Mean value of n = 3*				
	4 hr.	8 hr.	24 hr.	48 hr.	72 hr.
2	0.00	0.23	7.89	32.82	64.17
3	0.798	4.46	29.6	68.9	103.1
4	0.805	4.87	32.6	74.7	113.2

* Skin: Human epidermis, skin from female breast

Formula 2: 5 wt.% of fentanyl in a neutral polyacrylate adhesive containing 5.2% of free hydroxyl groups

Formula 3:

Fentanyl	5.0%
Polyacrylate adhesive, neutral, with 5.2% of hydroxyl groups	55.0%
Polypinene	15.0%
Glycerol	10.0%
Dioctyl cyclohexane	15.0%

Formula 4: 5 wt.% of fentanyl in a polyacrylate adhesive without free functional groups.

The results of the permeation study show that the rate of permeation can be significantly improved by the addition of substances that reduce the solubility of the active ingredient in the matrix. Approximately the same results are obtained with the use of an adhesive without free functional groups, which also has a low dissolving capacity for the active ingredient without additives.

The particular TTS sizes can be calculated for different TTS potencies from the permeation data. The results are listed in Table 4.

Rate of release	Calculated areas [cm²]				
	Formula 1	Formula 2*	Formula 2**	Formula 3	Formula 4
25 µm/hr.	513	63.7	28.1	17.45	15.9
50 µm/hr.	1,026	127.4	56.2	34.9	31.8
75 µm/hr.	1,539	191.1	84.3	52.35	47.7
100 µm/hr.	2,052	254.8	112.4	69.8	63.6

* calculated on the basis of the permeation data from Table 1

** calculated on the basis of the permeation data from Table 2

The result of the calculation shows that adhesives containing carboxyl groups lead to TTS that are too large for practical use at a fentanyl concentration of 5% even at the lowest dose. Even though the calculations lead to a rather large TTS even in the case of the adhesives containing hydroxyl groups, it is possible here to obtain a TTS of a size suitable for practical use if the concentration is not too high, e.g., at most 20%, by increasing the fentanyl concentration. It can be assumed in a simplified manner that the thermodynamic activity and consequently also the permeation rates depend linearly on the concentration as long as the active ingredient is present in the completely dissolved form.

By using solubility-lowering inactive ingredients in formulations with polyacrylate adhesives containing hydroxyl groups or by using polyacrylate adhesives without free functional groups, TTS that have an acceptable size even at the highest dosage of 100 µg/hr. at a fentanyl concentration of 5.0% are obtained. It is, of course, also possible in this case to further reduce the size of the system by increasing the fentanyl concentration.

As was mentioned in the introduction, fentanyl and its derivatives have a low therapeutic index. This means that, on the one hand, a certain threshold value is needed for the action, which must be exceeded in terms of the concentration in the plasma, but, on the other hand, unacceptable side effects will appear in a short time at higher concentrations. It is therefore advantageous for the system to additionally contain a control membrane, as a result of which the system limits the flow of active ingredient through the skin to a maximum regardless of the individual properties of the skin. Such membranes preferably consist of a copolymer made of ethylene and vinyl acetate (EVA polymer) or are microporous films based on polyethylene or polypropylene. Such membranes belong to the state of the art. In the case of the EVA polymers, the permeability to the active ingredient depends on the percentage of vinyl acetate and the thickness of the membranae. Membranes with a VA content between 2 wt.% and 25 wt.% and a thickness between 25 µm and 100 µm and preferably between 40 µm and 100 µm are common, but the vinyl acetate content and the thickness are not subject practically to hardly any limitations. Both parameters must be selected correspondingly for the particular formulation in order to guarantee the limitation to the desired maximum flow from the TTS. In the case of the microporous membranes, the substance is not transported by the polymer, but only by the pores located in these membranes. The number and the size of the pores determines the maximum rate of release of the TTS.

Such membranes are usually provided with an adhesive film to attach the TTS to the skin. Adhesive films based on self-adhesive polyacrylates or self-adhesive polysiloxanes are especially suitable for fentanyl and its derivatives. The advantage of polysiloxanes is that the active ingredient is very

... the TTS by the use of an additional adhesive film. However, such adhesive films may also be used in systems which contain no membranes but matrix layers with low adhesive power.

As in any TTS, it is, of course, possible in this case as well to reduce the barrier properties of the human stratum corneum by the use of permeation-enhancing substances. Such substances are, e.g., fatty acids, fatty alcohols, fatty acid esters, esters of glycerol with medium- and long-chain fatty acids and glycols such as 1,2-propanediol. All the substances that are physiologically harmless and are compatible with the active ingredient and the other inactive ingredients may be used.

It can be stated in summary that matrix systems according to the present invention show satisfactory to good rates of permeation and also make it possible to prepare TTS of an acceptable size. At the same time, the exposure of the patient to risk due to the absorption of an excessively large quantity of active ingredient as a consequence of leak is impossible. On the whole, matrix systems based on polyacrylate adhesives according to the present invention for fentanyl and its analogs represent a significant progress over the known state of the art in terms of patient safety.

Example 1 (Formulations 1, 2 and 4):

Fentanyl (free base) is dissolved in the solution of the adhesive in heptane/ethyl acetate. The quantity of fentanyl is calculated such that a concentration of 5.0% will be obtained relative to the solids content of the adhesive solution. The resulting mass is coated with a doctor blade on a siliconized polyester film [()protective layer to be removed before use()] in such a thickness that a coating weight of about 80 g/cm^2 will be obtained after the removal of the solvent. After the solvent has been removed, the dried film is laminated with a thin polyester film (backing layer of the TTS), and the finished TTS are cut out of the total laminate.

Example 2 (Formulation 3):

5.0 g of fentanyl, 15.0 g of polypinene, 10.0 g of glycerol, 15.0 g of dioctyl cyclohexane and 110 g of the adhesive solution with a solids content of 50.0% are combined and stirred until the fentanyl is dissolved. The resulting mass is coated with a doctor blade on a siliconized polyester film (protective layer to be removed before use) in such a thickness that a coating weight of about 80 g/m^2 will be obtained after the removal of the solvent. After the solvent has been removed, the dried film is laminated with a thin polyester film (backing layer of the TTS), and the finished TTS are cut out of the total laminate.

1. Transdermal Therapeutic System (TTS) comprising a backing layer impermeable to the active ingredient, at least one matrix layer based on polyacrylate which contains fentanyl or an active ingredient analogous to fentanyl and is based on polyacrylate, and a protective layer to be removed before use, <u>characterized in that</u> the polyacrylate is self-adhesive and free of carboxyl groups and has a saturation solubility for fentanyl of 3 wt.% to 20 wt.%, preferably a saturation solubility of 4 wt.% to 12 wt.% and especially preferably a saturation solubility of 5 wt.% to 10 wt.%, and that the layers containing the active ingredient contain at least 80 wt.% of the active ingredient incorporated in the molecularly dispersed dissolved form.

2. TTS in accordance with claim 1, characterized in that the polyacrylate polymer has no free functional groups and is formed only from monomers of the acrylic acid or methacrylic acid esters and optionally additionally other polymerizable vinyl compounds without free functional groups in quantities of up to 50 wt.%, and especially vinyl acetate.

3. TTS in accordance with claim 1, characterized in that the monomer mixture on which the polyacrylate is based contains up to 20 wt.% of monomers with free functional groups in the form of 2-hydroxyethyl acrylate and/or 2-hydroxyethyl methacrylate.

4. TTS in accordance with one or more of the claims 1-3, characterized in that it additionally contains a control membrane as an additional layer.

5. TTS in accordance with claim 4, characterized in that it additionally contains a self-adhesive layer located on the membrane toward the skin for attaching to the skin.

6. TTS in accordance with claim 4 or 5, characterized in that the control membrane consists of an ethylene-vinyl acetate copolymer, expediently with a vinyl acetate content of up to 25 wt.% or a microporous film based on polyethylene or polypropylene and it expediently has a thickness of 25 μm to 100 μm and preferably 40 μm to 100 μm.

7. TTS in accordance with one or more of the claims 1-6, characterized in that the layers containing the active ingredient additionally contain substances improving the rate of permeation through human skin, especially glycols and/or those belonging to the group of the fatty acids, fatty acid esters, fatty alcohols or glycerol esters.

8. TTS in accordance with one or more of the claims 1-7, characterized in that the layers containing the active ingredient contain substances that lower the solubility of the active ingredient in these layers.

9. TTS in accordance with claim 8, characterized in that the substances lowering the solubility are hydrocarbons that are liquid at room temperature, such as dioctyl cyclohexane or liquid paraffin, hydrocarbon resins such as polypinene resins or polyethylene glycol or glycerol.